REMARKS

Claims 83-87 were pending in the present application. Claims 83 and 85-87 have been amended herein. No new matter has been added. Upon entry of the present amendment, claims 83-87 will remain pending. **Because the amendments to the claims remove issues for appeal (*i.e.*, written description and obviousness rejections), Applicants respectfully request that they be entered into the record. See, M.P.E.P. §714.12.**

Applicants thank the Examiner for interviewing the present application on April 26, 2006, in which the differences between the present invention and the references of record were discussed among Herb Boswell (representative of Isis Pharmaceuticals, Inc.) and Examiners Marjorie Moran and Ardin Marschel.

I. The Claimed Invention Is Supported by Ample Written Description

Claims 83-87 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The thrust of the Examiner's argument presented in the Office Action is that Applicants' specification allegedly does not teach a computer system that first prepares a virtual library of oligonucleotide sequences and then reduces the number of sequences. Although Applicants disagree, solely to advance prosecution of the present application, Applicants have amended the claims herein to reflect the discussion during the interview on April 26, 2006.

Claim 83 is an exemplary claim for purpose of discussion. In particular, claim 83 has been amended to recite that the computer system: 1) "generates a list of oligonucleotide sequences according to a desired oligonucleotide length, thereby generating a series of oligonucleotide sequences" (support for which can be found at, for example, page 19, lines 10 to 25 of the specification); 2) "applies a virtual oligonucleotide chemistry to the oligonucleotide sequences generated in step i) to yield a set of virtual oligonucleotides" (support for which can be found at, for example, page 19, lines 26 to 29 of the specification); 3) "generates a subset of said set of virtual oligonucleotides based on targeting a functional region of said selected nucleic acid" (support for which can be found at, for example, page 24, line 34 to page 25, line 34 of the specification); and 4) "generates synthesis instructions in computer manipulable form for said oligonucleotide sequences in said subset of said set of virtual oligonucleotides" (support for

which can be found at, for example, page 26, line 23 to page 52, line 18 of the specification).

Applicants' specification contains ample basis for the claims as amended herein. No new matter has been added to the claims. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly providing new matter be withdrawn.

II. The Claimed Invention Is Not Obvious

Claims 83 and 85-87 and are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of the following references: 1) U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis reference"), 2) Hyndman et al., Biotechniques, 1996, 20, 1090 (hereinafter, the "Hyndman reference"), 3) Nickerson et al., Proc. Natl. Acad. Sci., 1990, 87, 8923 (hereinafter, the "Nickerson reference"), and 4) U.S. Patent No. 6,127,191 (hereinafter, the "Graybill reference").

Claims 83-87 also are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of the following references: 1) the Agrafiotis reference, 2) the Hyndman reference, 3) the Nickerson reference, 4) U.S. Patent No. 5,352,775 (hereinafter, the "Albertsen reference"), 5) U.S. Patent No. 5,407,796 (hereinafter, the "Cutting reference"), and 6) the Graybill reference.

The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to generate a virtual library of compounds in the system of Agrafiotis, Hyndman, and Nickerson (also taking into consideration the Albertsen and/or Cutting references) where the motivation would have been to select compounds for synthesis which best reflect the desired properties (Graybill). Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to combine the cited references and, even if combined, the claimed invention would not be produced.

Applicants' claimed invention differs from the Agrafiotis reference because, *inter alia*, the Agrafiotis reference describes generating a directed diversity chemical library where the number of compounds must increase with each iteration since additional compounds are synthesized for a new directed diversity chemical library. Further, at no point does the Agrafiotis

reference, alone or in combination with the Hyndman and/or Nickerson references, describe generating a set of virtual oligonucleotides, and then generating a subset of the set of virtual oligonucleotides using the criteria recited in the instant claims, followed by synthesis of only those compounds that remain following the reduction step. The addition of the Albertsen and/or Cutting references also fails to teach or suggest generating a set of virtual oligonucleotides followed by generating a subset of the set of virtual oligonucleotides using the criteria recited in the instant claims. Rather, the Agrafiotis reference teaches synthesizing and testing all members of the library as actual compounds once the chemical building blocks are selected. In the Agrafiotis process, initialization occurs by selecting a particular set of chemical building blocks "aimed at maximizing the information content of the resulting chemical library" (see, col. 16, lines 64-66). Once selected, the selected building blocks are combined to physically synthesize all combinations of the compounds (see, col. 5, lines 31-45; col. 22, lines 13-40). Thus, the Agrafiotis reference teaches physically synthesizing all compounds during initialization so that the number of oligonucleotide sequences in a virtual library is not reduced prior to synthesis. The synthesized compounds are analyzed to obtain structure-activity data (SAR) (see, Fig. 2; col. 5, lines 56-64), and the collected SAR and historical SAR are subsequently used to synthesize additional compounds for a new directed diversity chemical library (see, Fig. 2; col. 6, lines 49-53; col. 22, lines 41-67; col. 23, lines 1-30).

In contrast, Applicant's claimed invention relies on a system that first generates a list of oligonucleotide sequences according to a desired oligonucleotide length, thereby generating a series of oligonucleotide sequences; applies a virtual oligonucleotide chemistry to the oligonucleotide sequences generated previously to yield a set of virtual oligonucleotides; generates a subset of the set of virtual oligonucleotides based on targeting a functional region of the selected nucleic acid; and generates synthesis instructions in computer manipulable form for the oligonucleotide sequences in the subset of the set of virtual oligonucleotides.

The Hyndman reference does not cure the above-noted deficiencies in the Agrafiotis reference because the Hyndman reference, alone or in combination with the Agrafiotis reference, and the Nickerson reference, fails to teach or suggest all the elements recited in the claims. The Hyndman reference reports a computer program (HYB*simulator*) that uses input criteria such as

melt temperature, free energy and length to design a probe set against a target sequence, but then identifies preferred probes by eliminating sequences with insufficient target specificity (see, pages 1092, 1094, and Figure 4), or retaining probes expected to perform well in PCR amplifications. The Hyndman process does not teach or suggest generating a set of virtual oligonucleotides followed by generating a subset of the set of virtual oligonucleotides using the criteria recited in the instant claims, i.e., based on targeting a functional region of the selected nucleic acid as recited in claim 83, nor reduction by a process of selection based on i) target accessibility to the selected nucleic acid, ii) uniform distribution of oligonucleotide compounds across the selected nucleic acid, or iii) targeting a functional region of the selected nucleic acid as recited in claims 85-87. Thus, the Hyndman reference, alone or in combination with the Agrafiotis reference, does not teach or suggest all the elements of the claimed invention.

Further, the Nickerson reference merely reports testing of oligonucleotides using automated apparatus.

Thus, the combination of the Agrafiotis, Hyndman, and Nickerson references (and additionally the Albertsen and Cutting references) fails to produce Applicants' claimed invention.

The Office Action mistakenly takes the position that that the addition of the Graybill reference cures the deficiencies of the combination of the Agrafiotis, Hyndman, and Nickerson references (and the additional Albertsen and Cutting references). In particular, the Office Action asserts that the "DirectedDiversity®" program of the Graybill results in selection of compounds with desired properties wherein a virtual library of compounds is generated and then evaluated for specific physical and biological properties (referring to col. 14, lines 40-61). The Office Action, however, has taken this portion of the Graybill reference out of context. Indeed, the "DirectedDiversity®" program referred to in the portion of the Graybill reference referred to in the Office Action does not appear to carry out the process recited in claim 83, for example. Claim 83 recites that the computer system i) generates a list of oligonucleotide sequences according to a desired oligonucleotide length, thereby generating a series of oligonucleotide sequences; ii) applies a virtual oligonucleotide chemistry to the oligonucleotide sequences generated in step i) to yield a set of virtual oligonucleotides; iii) generates a subset of the set of

virtual oligonucleotides based on targeting a functional region of the selected nucleic acid; and iv) generates synthesis instructions in computer manipulable form for the oligonucleotide sequences in the subset of the set of virtual oligonucleotides. Rather, the "DirectedDiversity®" program of the Graybill reference is "an iterative drug refinement process that explores chemical space through successive rounds of sublibrary selection" (see, col. 14, lines 40-42). Further, the Graybill reference teaches that "if a first iteration of screening results in an active compound that contains a phenyl ring, then in subsequent iterations of the screen this aromatic residue can be varied using substituted phenyl groups in a stepwise manner" (see, col. 14, lines 33-37). The Graybill reference further teaches that a "preferred iterative method is DirectedDiversity®." Thus, there is no teaching whatsoever in the Graybill reference of any process that "generates a subset of said set of virtual oligonucleotides based on targeting a functional region of said selected nucleic acid" as recited in claim 83. Generation of the subset, as recited in claim 83, reduces the number of oligonucleotide sequences in the virtual library of oligonucleotide sequences based on targeting a functional region of the selected nucleic acid. Indeed, the DirectedDiversity® program in the Graybill reference is used to prepare aminobenzenedicarboxylic acid-based combinatorial libraries wherein the iterations are carried out to refine particular chemical groups, such as phenyl groups, within the aminobenzenedicarboxylic acid compounds, **not** to reduce the number of oligonucleotide sequences in a virtual library of oligonucleotide sequences by a process of selection based on **targeting a functional region** of the selected nucleic acid. Thus, the addition of the Graybill reference to the combination of the Agrafiotis, Hyndman, and Nickerson references (and additionally the Albertsen and Cutting references) fails to produce Applicants' claimed invention.

Furthermore, Applicants respectfully submit that the proposed modification (i.e., generating a subset of the set of virtual oligonucleotides based on targeting a functional region of a selected nucleic acid) to the Agrafiotis reference is improper because it renders the Agrafiotis reference unsatisfactory for its intended purpose. Indeed, Agrafiotis' invention relies on synthesizing and collecting data using a set of compounds, followed by iteration and synthesis of additional compounds based on structure activity relationship data obtained from the initial set.

As the Agrafiotis reference teaches, an initial set of building blocks is selected for making a directed diversity library. Those building blocks are selected to provide maximum information content:

> The initial choice is aimed at maximizing the information content of the resulting chemical library within the domain of interest, as measured by the presence of chemical functionalities, hydrogen bonding characteristics, electronic properties, topological and topographical parameters.

(the Agrafiotis reference at col. 16, line 64 to col. 17, line 2). Because the proposed modification to reduce *in silico* the members of the directed diversity library according to the criteria recited in the instantly claimed invention interferes with Agrafiotis' requirement to derive structure-activity models having enhanced predictive and discriminating capabilities it renders Agrafiotis unsatisfactory for its intended purpose, thus seriously undermining the Examiner's alleged reasons for motivation. The motivation therefore is improper. See, MPEP §2143.01.

Thus, the combination of the Agrafiotis, Hyndman, Nickerson, and/or the Albertsen and Cutting references with the addition of the Graybill reference does not disclose generating a subset of the set of virtual oligonucleotides based on i) target accessibility to the selected nucleic acid, ii) uniform distribution of oligonucleotide compounds across the selected nucleic acid, or iii) targeting a functional region of the selected nucleic acid. Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

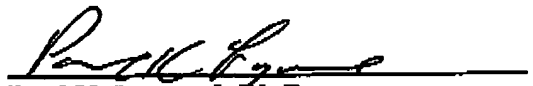
III. Obviousness-Type Double Patenting

Claims 83 and 85-87 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 55, 56, 58-72, 74-87, and 99-102 of co-pending application Serial No. 09/295,463. Applicants enclose herewith a terminal disclaimer.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,



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